PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 58098-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT//US0/3/23978	International filing date *(day/month/year)* 01 August 2003 (01.08.2003)	Priority date *(day/month/year)*
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 43/04; A61K 31/70, 38/00, 51/00; C07H 21/04; and US Cl.: 514/2, 44; 435/6, 325, 375, 458; 536/24.5; 424/1.11		
Applicant CARITAS ST. ELIZABETH'S MEDICAL CENTER OF BOSTON, INC..		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2\ March 2004 (2\ .03.2004)	19 December 2005 (19.12.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Janet L. Epps-Ford Telephone No. (571)272-0500

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT//US0/3/23978

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-53 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 54-62, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-16, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 4-7,10-16,20-29,35,46-68 and 70-74	YES
	Claims 1-3, 8-9, 17-19, 30-34, 36-45, and 69	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-74	NO
Industrial Applicability (IA)	Claims 1-74	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-3, 8-9, 17-19, 30-34, 36-45, and 69 lack novelty under PCT Article 33(2) as being anticipated by Sawada et al.

Claim 1 recites a method for modulating endothelial cell proliferation in a mammal, wherein the method comprises increasing or decreasing ezrin activity in the mammal by an amount sufficient to modulate proliferation of the cells.

Sawada et al. describe a study using Y-27632 and dominant-negative ROCK. This reference describes ROCK as a key regulator of vascular contraction, and controls vascular growth in vitro and in vivo. This reference concludes that the inhibition of ROCK (particularly by Y-27632) may be a potential therapeutic strategy for treating vascular proliferative disorders and hypertension (see conclusions §, page 2030).

Claims 1-74 lack an inventive step under PCT Article 33(3) as being anticipated by Sawada et al. in view of Perez.

As stated above, Sawada et al. describe a study using Y-27632 and dominant-negative ROCK. This reference describes ROCK as a key regulator of vascular contraction, and controls vascular growth in vitro and in vivo. This reference concludes that the inhibition of ROCK (particularly by Y-27632) may be a potential therapeutic strategy for treating vascular proliferative disorders and hypertension (see conclusions §, page 2030).

Sawada et al. does not teach the relationship between the Rho dependent kinase (ROCK) and ezrin.

Perez et al. teach that ezrin activation is dependent upon the activity of the Rho-dependent kinase (see page 59). Perez et al. teach that Y-27632 functions as an inhibitor of ezrin phosphorylation (see page 57, 2nd col. 2nd paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention, to have combined the teachings of Sawada et al. and Perez et al. to comprise a method for modulating endothelial cell proliferation in a mammal, wherein the method comprises increasing or decreasing ezrin activity in the mammal by an amount sufficient to modulate proliferation of the cells. One of ordinary skill in the art would have been motivated to make this modification since, the methods of Sawada et al. clearly teach the administration of Y-27632 for the suppression of neointimal formation of balloon injured arteries, and Perez et al. teach that Y-27632 is also an inhibitor of ezrin activation. Therefore, the methods of Sawada et al. inherently comprise a method for modulation cell proliferation comprising inhibiting ezrin activation via the activity of administered Y-27632.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-8, 10-33, 35-74 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: The claims are broadly drawn to methods that comprise an in vivo method of treating an unspecified condition associated with ezrin activity by administering an unspecified agent that modulates the expression of ezrin. However, due to the broad number of potential compounds that may function to modulate the expression of ezrin and the limited guidance provided in the specification as filed, the skilled artisan would have to resort to de novo undue experimentation in order to practice the full scope of the claimed invention. This experimentation would include determining what conditions are treatable via the administration of ezrin modulators, identifying the structures of the full scope of these ezrin modulators, modes of delivery such that a sufficient amount of ezrin modulator is delivered to the appropriate tissues, at a sufficient period of time such that ezrin is modulated to such a degree that treatment effects are observed. Neither the specification as filed, nor the state of the prior art provides the required specific guidance to practice the full scope of the claimed invention.